

## **REMARKS**

This submission includes the arguments and amendments filed in response to the Final Office Action mailed on March 29, 2007. According to the Advisory Action Before the Filing of an Appeal Brief mailed on July 31, 2007 the amendments were not entered and the evidence presented was not considered.

Claims **1, 3-39, 49-52, 55-62** and **70-96** are pending in the application. Claims **2, 12-17, 21-31, and 39-96** are cancelled.

Claims **1, 3-5, 32-36** and **38** are rejected. Claims **6-11, 18-20** and **37** are objected.

Claims **5, 18, and 33** are currently amended. Claims **34, 35, 36** and **38** are currently withdrawn.

### **Objections**

Claim **18** is objected because of informalities. Claim **18** has been amended and it shows “and” instead of “andkl”.

Claim **5** is objected under 37 CFR 1.75(c). Claim **5** has been amended to remove species not within the scope of claim 1.

Claims **6-11, 18-20** are objected as being dependent upon a rejected base claim. Applicants trust that the remarks directed to the rejection of claims **1, 3, 4, 5, and 32** under 35 U.S.C. § 103(a) will overcome the rejection and therefore claims **6-11, 18-20** will be allowed.

### **Rejections under 35 U.S.C. § 112, second paragraph**

Claims **5** and **11** are rejected under 35 U.S.C. § 112, second paragraph for being indefinite. The Office Action indicates that these claims have been made dependent on “claim 41”. Applicants submit that “41” was actually a 4 which was stricken but the strikethrough line was not evident, and the 1, was the new claim number. In fact claims **5** and **11** were previously dependent on claim 4, and by amendment became dependent on claim 1. Now that the amendment has been accepted, claim **5** and **11** both are clearly shown as dependent on claim 1.

### **Rejections under 35 U.S.C. § 112, first paragraph**

Claims **33-36** and **38** remain rejected under 35 U.S.C. § 112, first paragraph, for the reasons stated on record. Applicants have amended claim **33** to limit the sexual

dysfunction to male sexual dysfunction. To expedite prosecution, claims **34, 35, 36** and **38** are withdrawn.

Rejections under 35 U.S.C. § 103(a)

Claim **1, 3, 4, 5**, and **32** remains rejected under 35 U.S.C. § 103(a) as being unpatentable over Buzas (GB '523) in view of Buzas (GB'080) for reasons of record. .

Applicants reiterate the arguments presented in the last replies dated December 22, 2006, and June 29, 2007. GB'523 discloses compounds of formula (I) of the instant application wherein R<sub>1</sub> is allyl, L is (CH<sub>2</sub>)<sub>3</sub>, and R<sub>4</sub> is 2-pyridyl or 2-pyrimidinyl. GB'080 discloses compounds wherein R<sub>1</sub> represents lower aliphatic hydrocarbyl group, etc., L is (CH<sub>2</sub>)<sub>1-3</sub>, and R<sub>4</sub> is phenyl. Both references disclose using the compounds as anti-inflammatory agents and made no mention of Applicants' use of treating sexual dysfunction. In order to arrive at claims 3, 4, and 5 of the present application, one would have substituted the phenyl group in GB'080 (R<sub>3</sub>) with 2-pyridyl of the present application. There was no indication or teaching in the prior art to make such substitution. Neither did the Examiner provide reasons why one skilled in the art would make such a substitution and derive at Applicant's invention. The genus in GB'080 includes thousands of compounds. Although the definition of lower aliphatic hydrocarbyl group for R<sub>1</sub> include alkyl and alkenyl, of all 26 examples listed in Table II of GB'080, only allyl and propargyl were shown and none has an alkyl substituent for R<sub>1</sub>. In the area of Medicinal Chemistry where unpredictability of biological activity associated with minor changes are well documented, it is not known if placing alkyl on the R<sub>1</sub> position and replacing the phenyl group with 2-pyridyl group on the R<sub>4</sub> position will result in Applicants' invention. Phenyl is not equivalent to 2-pyridyl, the latter contains a nitrogen atom possibly exerting influence with its lone pair electrons on the configuration and shape of the molecule, hence may affect the binding ability to a particular receptor. The prior arts offer no guidance to one of ordinary skill to the art to such a particular subset wherein R<sub>1</sub> is alkyl and R<sub>4</sub> is 2-pyridyl. Moreover, GB '523 and GB'080 offer no basis to reasonably expect that such changes would yield an active D4 agonist. Applicants are presenting evidence that demonstrates that claimed compounds having phenyl group on R<sub>4</sub> were unexpectedly less potent than those with 2-pyridyl as R<sub>4</sub> substituent, and that R<sub>1</sub> as allyl group was less desirable than R<sub>1</sub> as alkyl. This evidence

was not previously presented, as Applicants did not anticipate that the results in said article would be needed as evidence to prove the remarkable properties of the compounds of the invention. This evidence is presented as article titled "*1-Aryl-3-(4-pyridine-2-yl)piperazin-1-yl)propan-1-one Oximes as Potent Dopamine D<sub>4</sub> Receptor Agonists for the Treatment of Erectile Dysfunction*" published in the Journal of Medicinal Chemistry, Vol. 49, pages 5093 to 5109 (2006). Examiner is respectfully directed to Table 3 (page 5097), which indicates the striking difference in EC<sub>50</sub> between compounds with phenyl and compounds with 2-pyridine. Furthermore, instant application recites L being C<sub>1</sub>-C<sub>2</sub> alkylene; while C<sub>1</sub>-C<sub>2</sub> is a subgenus of C<sub>1</sub>-C<sub>3</sub> disclosed in GB'080, Applicants submit that this article demonstrates that compounds with C<sub>1</sub>-C<sub>2</sub> linker are more selective in D<sub>4</sub> agonist activity over D<sub>2</sub> agonist activity than those containing a C<sub>3</sub> linker. Table 2 (page 5096) indicates that L as C<sub>1</sub>-C<sub>2</sub> is preferred over other longer substituents.

Discovering which combination of variables is required for the utility possessed by compounds of instant application is arduous and uncertain. Combinations of variables of R<sub>1</sub>, L and R<sub>3</sub> to derive at Applicants' claimed compounds are a result of experimentations on the part of Applicants and not merely substituting one element recited in one reference with another element disclosed in another reference.

## **Conclusions**

In view of the foregoing amendments and arguments, Applicants respectfully submit that the claims in the present application are patentable over the prior art and request allowance of the same.

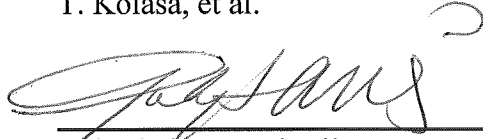
Should the Examiner have any concerns regarding the above, the Examiner is respectfully requested to contact the undersigned at the telephone number listed below.

Please charge deposit Account 01-0025 in the amount of \$790.00 to cover the cost of the Request for Continued Examination (RCE).. The Commissioner is hereby authorized to charge any additional Filing Fees required under 37 CFR 1.16, as well as any patent application processing fees under 37 CFR 1.17 associated with this communication for which full payment has not been tendered to Deposit Account No.

01-0025. Any deficiency or overpayment should be charged or credited to the above-numbered deposit account.

Respectfully submitted,  
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